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| EXAMINER |
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MINNIFIELD, NITA M

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1645

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07/27/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/817,165

Applicant(s)

KRIEG ET AL.

Examiner

N. M. Minnifield

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 April 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

1. Applicants' amendment filed April 30, 2007 is acknowledged and has been entered. Claims 1-18 have been canceled. Claim 19 is now pending in the present application. All rejections have been withdrawn in view of Applicants' amendment to the claims and/or comments, with the exception of those discussed below.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claim 19 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-11 and 13-30 of copending Application No. 09/818918. Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim and disclose methods of treating dermatitis or allergic reactions comprising administering to the subject a composition comprising an immunostimulatory oligonucleotide or immunostimulatory oligonucleotide and allergen.

It is also noted that Applicants have filed numerous related applications and that there could potentially be other double patenting rejections. Applicants are encouraged to apprise the Examiner of all applications that claim the same or similar subject.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The provisional obviousness-type rejection is maintained for the reasons of record. In the Remarks filed April 30, 2007, Applicants elect to defer substantive rebuttal until the above-identified conflicting claims are allowed. The rejection is maintained. It is noted that 09/818918 has been allowed.

4. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating an allergic response to an antigen or allergy related disorder during antigen specific immunotherapy of a subject comprising administering to a subject during antigen specific immunotherapy a composition comprising CpG, SEQ ID NO: 10 and antigen (administering a first and second composition), does not reasonably provide enablement for treating an allergic response to any antigen comprising administering to a subject during antigen specific immunotherapy any immunostimulatory oligonucleotide CpG, of *any* size and an antigen (administering a first and second composition). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The claims are directed to a method of treating an allergic response or allergy related disorder (i.e. atopic dermatitis, allergic dermatitis, etc) comprising administering to a subject during antigen specific immunotherapy a composition comprising a CpG oligonucleotide and antigen (i.e. allergen), as well as administering a first and second composition (CpG and antigen). The CpG oligonucleotide can be of *any* size or formula; the only requirement is that it contain 5' *CpG* 3'.

The specification discloses Example 12 (see p. 51), prevention of the development of an inflammatory cellular infiltrate and eosinophilia in a murine model of asthma. Mice were immunized with *Schistosoma mansoni* eggs (SEA) by i.p. injection on days 0 and 7. SEQ ID NO: 10 was administered to the immunized mice and soluble SEA was administered by intranasal instillation on days 14 and 21. After challenge the mice were sacrificed and cytokine levels and other assays conducted on the lavage fluids. The specification indicates that Figures 9-15 show that CpG/SEA induced inflammatory cells, eosinophils, to be present and generated macrophages; higher IL-12 was induced, IL-4 was reduced and IFN-gamma production increased. Applicants assert that the CpG redirected the cytokine response of the lung to production of IFN-gamma, indicating a Th1 type immune response (p. 52).

The specification does not teach that any of the other myriad of possibilities of CpG of *any* size or formula can be used to treat any allergic response or allergy related disorder (i.e. allergic asthma, rhinitis, conjunctivitis, eczema, atopic dermatitis) in a subject. The results shown for asthma do not indicate that an immunostimulatory oligonucleotide (CpG oligonucleotide of 8 nucleotides in length or greater or less than 8 nucleotides) enables the method treating an allergic response in a subject as instantly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

A review of the specification discloses a list of immunostimulatory nucleic acids that could be used in the claimed invention. However, they comprise 8 or more nucleotides (see for example Tables 1, 2, 5, 9, 10), the instant claim only indicates that a C and G (CpG) are required. It is noted that Applicants'

specification indicates that ODNs shorter than 8 bases were non-stimulatory (p. 19).

The state of the art is unpredictable with regard to the use of oligonucleotides of less than 8 nucleotides having immunostimulatory activity. Yamamoto et al 1994 (Antisense Research and Development, 1994, 4:119-122) teaches that “immunostimulatory activity of oligonucleotides 18 bases or more in length was observed and was proportional to the base length, with a maximum at 22-30 bases. On the other hand, the oligonucleotides 16 bases or less in length were not as active even if they possessed the palindromic sequences. These results indicate that the immunostimulatory activity of oligonucleotides with certain palindromic sequences requires an oligonucleotide at least 18 bases long.” (abstract). The state of the art with regard to the CpG oligonucleotides and stimulating a Th-1 immune response (treating an allergic response to an antigen or allergy related disorder during antigen specific immunotherapy of a subject) is unpredictable. The state of the art teaches that there are a number of specific characteristics of the oligonucleotide, which are critical for its function as an immunostimulatory molecule. For instance, Kreig (BioDrugs 1998, 5:341-346) teaches that synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was only a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by s-methyl-cytosine, then the oligonucleotide lost its immune stimulatory activity (p. 342). Yamamoto et al 1994 (Antisense Research and Development, 1994, 4:119-122) teaches that “immunostimulatory activity of oligonucleotides 18 bases or more in length was observed and was proportional to the base length, with a

maximum at 22-30 bases. On the other hand, the oligonucleotides 16 bases or less in length were not as active even if they possessed the palindromic sequences. These results indicate that the immuno-stimulatory activity of oligonucleotides with certain palindromic sequences requires an oligonucleotide at least 18 bases long." (abstract). Agarwal et al. (Trends in Mol. Med., 2002; 8:114-121) teaches that the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (see page 16 "therapeutic potential of CpG DNA" in particular) and that there is a species-dependent selectivity of CpG DNA, and that the optimal CpG DNA sequences for many vertebrate species are not yet known (p. 119). Further, Agrawal et al. teach that "The presence of unmethylated CpG dinucleotide is essential for the induction of immuno-stimulatory activity..." (See p. 114, bottom of second column). Agrawal also teaches that sequences required for CpG related immune stimulation varies from species to species, and indicates, "The optimal motif for recognition by human immune cells is 'GTCGTT or TTCGTT" (p. 115). Thus indicating that an oligonucleotide of 6 nucleotides in length can function as an immunostimulatory agent in humans. Hartmann et al. (J. Immunology, 2000; 164:1617-1624) teaches that the oligonucleotide must be protected from nuclease degradation in order to be effective in vivo. Specifically, Hartmann teaches, "To have in vivo clinical utility,. ODN must be administered in a form that protects them against nuclease degradation. The native phosphodiester internucleotide linkage can be modified to become highly nuclease resistant via replacement of one of the non-bridging oxygen atoms with a sulfur, which constitutes phosphorothioate ODN." (see p. 1618). Therefore, in order for an oligonucleotide to stimulate an immune response

in vivo it must contain an unmethylated CpG motif, be at least 6 nucleotides in length, and be protected from nuclease degradation by comprising, for example, modified backbone linkage, such as a phosphorothioate linkage. Further, Van Uden et al (J. Allergy Clin. Immunol., 1999, 104:902-910) teaches that although “ISS are generally considered by researchers in this field to be modular 6-mer units, it has been difficult to determine the minimum stimulatory motif length. One study showed that a minimum length of 18 bases was required but that a length of 22 bases gave greater activity. Another study demonstrated good activity with a 15-mer ODN. Still another study used cationic lipid transfection to show a stimulatory effect with a 6-mer ODN.” (p. 904, col. 1) Van Uden et al teaches that each ISS appears to have a different minimum length because crucial flanking bases would be variably distant from the core (p. 904, col. 2).

The amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to practicing the claimed invention. Applicants have not provided guidance in the specification toward a method of treating the claimed allergy related disorders, atopic dermatitis or allergic dermatitis comprising the administration first and second compositions that comprise immunostimulatory nucleic acid, of *any* size or formula, and antigen. As previously stated the specification teaches an increase in immunomodulation in mice (and comprising conversion from a Th2 to a Th1 immune response), and treatment of asthma in a mouse model comprising the administration of SEQ ID NO: 10. One skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of the successful treatment of atopic dermatitis or allergic dermatitis or any allergy related disorder in any organism comprising the administration of first and second compositions (CpG of

any size and formula and antigen) by any route to a subject during antigen specific immunotherapy in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in any and/or all organisms. The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art associated with effects provided *in vivo* in any and/or all organisms upon administration via any route of any CpG containing oligonucleotides, and further whereby treatment effects are provided in any and/or all organism for atopic dermatitis or allergic dermatitis. The breadth of the claims is very broad and the quantity of experimentation required is undue. The quantity of experimentation required to practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the CpG to target appropriate cells and/or tissues in any and/or all organisms, and further whereby treatment effects are provided for the claimed conditions. Since the specification fails to provide particular guidance for the treatment of the claimed atopic dermatitis or allergic dermatitis or allergy related disorders comprising administration of first and second compositions (*any* CpG and antigen) by any route to a subject during antigen specific immunotherapy is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

With respect to linkage modifications, combinations thereof or ribose nucleotides or combinations with deoxynucleotides and complexed or linked to biodegradable carriers, Weiner (J. Leukocyte Biology, 68:456-463, 2000) states that the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood (see page 461). While the biological effects of some

chemical modifications have been studied for CpG containing oligonucleotides, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (see Agarwal et al, Molecular Med, Today, 6:72-81, 2000, especially pp 78-80). Further, the state of the art teaches that the phosphorothioate analogs are the most potent in immune stimulation (see Zhao et al (Biochemical Pharmacology, 51:173-182, 1996, page 173 (abstract) and there is no evidence of record that any sequence that is not fully phosphorothiolated provides for immune stimulation in any model.

Further, the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art and the level of skill in the art. The state of the art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The relative skill of those in the art refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. The specification must be enabling as of the filing date, not evidence provided several years after the date of filing. The state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date. (see MPEP 2164.05(a))

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (1) the breadth of the claims; (2) the

nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims is quite broad in view of the scope of the possible large number of immunostimulatory oligonucleotides that can be used in the claimed method. The nature of the invention and the state of the art has been described above. The level of one of ordinary skill is high (PhD level). The art is unpredictable as previously indicated. With regard to factors 6 and 7, the specification does not provide sufficient direction and the working examples do not enable the broad scope of the claimed immunostimulatory oligonucleotides used in the instantly claimed method. A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In view of all of the above, the pending specification does not enable the claimed invention and therefore the pending claims are not enabled. For reasons stated above (i.e. lack of enabling disclosure, unpredictability of the art, lack of guidance) it would require undue experimentation to practice the claimed invention.


5. No claim is allowed.

6. The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record in the related applications.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.


N. M. Minnifield
Primary Examiner
Art Unit 1645
7-23-07